GRÜNENTHAL USA, INC.

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August 5, 2005

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Via overnight courier

Division of Dockets Management
(HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 2005D-0203, CDER 200484. Draft Guidance for Industry on Safety Testing of Drug Metabolites; Availability. Page 32839 (FR Doc. 05-11205)

Dear Sir/Madam:

Grünenthal welcomes this new guidance and is fully supportive of its intent. We believe the document will provide industry with good guidance for safety assessments.

We would appreciate the FDA's considering including the clarifications stated in Attachment 1. Please note that we refer to the reference lines of the pdf document.

Thank you.

Sincerely,

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Development Regulatory Affairs
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Attachment 1
Proposed Changes to Guidance Document on Safety Testing of Drug Metabolites

Reference lines 27-31

evaluated as early as possible during the clinical development program. This guidance defines major metabolites primarily as those identified in human plasma that account for greater than 10 percent of drug related material (amount excreted vs. administered dose or AUC vs. systemic exposure whichever is more) and that were not present at sufficient levels to permit adequate evaluation during standard nonclinical animal studies.

Reference lines 71-73

Generally, we recommend that metabolites identified in human plasma that account for greater than 10 percent of drug related material (amount excreted vs. administered dose or AUC vs. systemic exposure whichever is more) be considered for safety assessment.

Reference lines 299-309

GLOSSARY

Major metabolite — A metabolite identified in human plasma, the AUC of which accounts for greater than 10 percent of the total systemic exposure, or which is excreted as more than 10% of the administered dose, whichever is more.

Metabolite — A compound derived from the parent compound through Phase I and/or Phase II metabolic pathways.

Pharmacologically active metabolite — A metabolite that has pharmacological potency at the target receptor that is greater than, equal to, or less than the parent compound.

Justification

The changes in lines 29, 30, 72, 73, 301, 302, and 303 clarify the 10% limit. Administered dose is given as mass; systemic exposure is given as time · mass / volume. Without this clarification the definition may be misunderstood.

The first change in line 301 prevents metabolites that are not present in plasma from being classified as "major".